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ORIGINAL ARTICLE

What Characterizes House Dust Mite Sensitive Individuals in a House Dust Mite Free Community in Reykjavik, Iceland?

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ABSTRACT

Background: Previous studies show that 6–9% of young adults in Reykjavik are sensitised to the house dust mite (HDM) *Dermatophagoides pteronyssinus* (*D. pteronyssinus*). However, only negligible amounts of HDM and HDM allergens were detected in their homes. The study investigates what characterizes these individuals.

Methods: We investigated all participants in the European Community Respiratory Health Surveys I and II (ECRHS I and II) with *D. pteronyssinus* specific IgE, in the years 1991–92. A grass positive but *D. pteronyssinus* negative control group was recruited from the same cohort. A detailed questionnaire was administered and the specific IgE (Pharmacia CAP system) against six *D. pteronyssinus* cross-reactive allergens was measured.

Results: Of 601 ECRHS I participants with available IgE results, 88% returned for ECRHS II, 8.4 years later. Of 49 individuals with *D. pteronyssinus* specific IgE in ECRHS I, 24 had become negative in ECRHS II. Compared with controls, HDM sensitive subjects were more often men who had lived on farms or kept aquaria fish in childhood. Of those with specific IgE against *D. pteronyssinus* in ECRHS I and II, 75% had detectable IgE antibodies ($\geq$0.35 kU/l) to cross-reactive allergens compared with none in the control group ($p < 0.0001$): *Lepidoglyphus destructor* (*L. destructor*) (67%), shrimp (58%), cockroach (33%), mosquito (17%), tropomyosin (17%) and blood worm (4%).

Conclusions: Icelanders with specific IgE to *D. pteronyssinus* are more often men who spent time on farms in childhood and today have high prevalence of IgE antibodies cross-reactive to *D. pteronyssinus*.

KEY WORDS

allergy, cross-reactivity, ECRHS, house dust mites, Iceland

INTRODUCTION

In the European Community Respiratory Health Survey I (ECRHS I) conducted in the years 1990–1991 the IgE sensitisation to *D. pteronyssinus*, measured by Pharmacia CAP System,[1] was 9% (IgE $\geq$0.35 kU/l) in a random sample of young adults in Reykjavik and suburbs.[2] By skin prick test (SPT) 6.1% were positive to *D. pteronyssinus*, using a cut off limit of 3 mm[3]. These findings in Reykjavik are comparable to the results in Uppsala Sweden, where corresponding figures were 7.9% and 7.4%, respectively.[3]

As a part of the ECRHS II indoors protocol (www.ecrhs.org) 197 randomly selected adults from ECRHS I were visited in their homes between March 2001 and January 2002. Dust samples were collected from their mattresses, according to the protocol, for measurement of house dust mite (HDM) allergen concentration and furthermore for the determination of the number and type of HDM.[4] Only two mites, both *D. pteronyssinus*, were found in two separate dust samples. Mite allergen analysis identified a mini-

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mal amount of Der f 1 in two dust samples taken from other homes. Additionally, samples were collected in November 2002 from mattresses and bedroom floors in homes of 10 HDM allergic patients, not included in ECRHS II. The samples were examined for mites only but no mites were found.[4] These results indicate that exposure to HDM in the Reykjavik area is extremely rare.

According to Korsgaard the risk of being sensitised to HDM in a cool temperate climate is assumed to be a consequence of indoor exposure.[5] Assuming this is right the question rises how people in Reykjavik with positive SPT or specific IgE to *D. pteronyssinus* have become sensitised and about its clinical relevance. Therefore we decided to investigate what characterized those individuals who had specific IgE to *D. pteronyssinus* in ECRHS I in comparison with individuals, from the same cohort, positive to grass pollen antigens, but with no antibodies to *D. pteronyssinus*.

METHODS

STUDY GROUPS

Of 601 participants in ECRHS I who provided blood for specific IgE, 529 (88.0%) participated in ECRHS II with a new blood sample. The participation rate in this cohort was substantially higher than average for all centres in ECRHS.[6] The median follow up time was 8.38 years. The mean age at ECRHS II was 41.7 years, women constituted 54% of the samples.[7] Of 58 with detectible *D. pteronyssinus* specific IgE in ECRHS I, 49 participated in ECRHS II and constitute our study population, of whom 25 were still positive to *D. pteronyssinus*, but 24 had become negative at that time point and 4 who were negative at ECRHS I had become positive in ECRHS II. They are not included in the study. A control group included participants with specific IgE to timothy grass in ECRHS II, but no IgE to *D. pteronyssinus*.

METHODS

The study population was divided into three groups (Table 1):

1) Individuals with *D. pteronyssinus* specific IgE, both in ECRHS I and II (group +/+).

2) Individuals with *D. pteronyssinus* specific IgE in ECRHS I, but not in ECRHS II (group +/–).

3) Individuals with timothy grass specific IgE at ECRHS II but negative on specific IgE to *D. pteronyssinus* at ECRHS I and II (group –/–).

DATA COLLECTION

All participants were contacted in 2004 and asked detailed questions about childhood environment, travelling abroad, farming, hobbies and allergic symptoms to shellfish and mosquito bites. Data from ECRHS II were also used in subsequent analyses, namely questionnaire data on respiratory symptoms, asthma and allergic symptoms in addition to spirometry results[8] and test results for bronchial responsiveness based on a methacholine challenge.[9]

IgE ANTIBODY MEASUREMENT

Total IgE was measured as a part of the ECRHS II protocol, specific IgE value to *D. pteronyssinus* and grass was measured both in ECRHS I and II, but frozen venous blood samples from ECRHS II were used to measure serum IgE antibodies to the following available antigens reported to cross-react to HDM; the storage mite *Lepidoglyphus destructor* (*L. destructor*), shrimp (*P. borealis*), cockroach (*B. germanica*), mosquito (*A. communis*), tropomyosin (tropomyosin Pen a 1) and blood worm (*C. thummi*) by an enzymatic immunoassay (CAP-FEIA) performed according to the manufacturer's instructions (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden). Results of $\geq$0.35 kU/l were considered positive. In ECRHS I *L. destructor* was included in the SPT panel.

The study design was approved by the local ethics committee.

STATISTICS

Mean values with 95% confidence intervals were used for continuous variables. The two-sided Fischer's exact test and two-sided student's *t*-test were used for comparison of groups. A p value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Of 89 individuals eligible in 2004, 79 (89%) could be reached and agreed to participate, 24 in group +/+, 20 in group +/–, and 35 in the control group (Table 1). Among the 44 subjects in groups +/+ and +/– with *D. pteronyssinus* specific IgE in ECRHS I, 20 (45%) had positive SPT to *L. destructor* at the same time, 12 in group +/+ and 8 in group +/–. One in the control group –/– had positive SPT to *L. destructor* in ECRHS I. In group +/+, 6 were exclusively positive to *D. pteronyssinus* in ECRHS II, when measured by specific IgE and only one of them had a positive SPT to *L. destructor* in ECRHS I.

There were significantly more men in the +/+ group than in the control group or 18 (75%) *vs.* 11 (31%) ($p < 0.01$). The mean age was comparable between the groups.

ALLERGY SYMPTOMS AND METHACHOLINE CHALLENGE TESTS

No difference was observed between the groups in terms of history of wheezing, asthma or history of eczema (Table 2). In group +/– 50% reported symptoms of nasal allergies, including hay fever, compared with 83% in the control group ($p < 0.05$). The grass sensitive control group reported significantly more allergic symptoms when exposed to pollens than the HDM

Table 1 Demographics of house dust mite (HDM) sensitive subjects and grass sensitive controls.

	HDM sensitive		Grass sensitive
	Group +/+	Group +/−	Group −/−
Demographic			
total number	25	24	40
responded	24	20	35
moved away	1	1	1
died	—	—	1
untracked	—	3	3
men (%)	75*	55	31
mean age (95% CI)	47 (44−50)	48 (44−52)	45 (42−47)

Group +/+: Individuals positive to *D. pteronyssinus* in ECRHS I and ECRHS II

Group +/−: Individuals positive to *D. pteronyssinus* in ECRHS I, but negative in ECRHS II.

Group −/−: Individuals neg. to *D. pteronyssinus* in ECRHS I and ECRHS II but positive to timothy grass in ECRHS II.

* $p < 0.05$, compared with the −/− group (Fisher's Exact Test)

groups ($p < 0.001$). Exposure to dust was not associated with more symptoms in the HDM sensitised subjects compared with the control group. Bronchial hyperresponsiveness (BHR) was measured by a methacholine challenge test using PD20 = 1.0 mg methacholine as a cut off level. There was a non-significant tendency for the control group to show a positive BHR more often, or 19% compared with 14% in group +/+ and 12% in group +/–. The mean forced expiratory volume in 1 second (FEV1), as a percentage (%) of predictive value, was 100, 103 and 101 for groups +/+, +/– and –/–, respectively.

CHILDHOOD AND ENVIRONMENTAL FINDINGS

The re-evaluation in 2004 revealed that significantly more subjects in group +/+ had lived on a farm during summer holidays as children or adolescents than in the control group ($p < 0.05$) (Table 3). Among those 6 in the +/+ group, solely positive to *D. pteronyssinus*, 5 had been on farms during the summer vacation as a children or adolescents. Living or travelling abroad was not different for the groups, but being an owner or caretaker of aquarium fishes before the age of 12 was more often associated with present HDM allergy ($p < 0.05$). Horse riding, clinical reactions from eating shellfish and reactions to mosquito bites were more commonly reported in the HDM allergic group but did not reach statistical significance (Table 3).

SERUM IGE MEASUREMENTS

Total serum IgE (geometric mean) was significantly higher in group +/+ than in the control group, 111 *vs.* 43 kU/l ($p < 0.01$). Specific IgE (geometric mean) to *D. pteronyssinus* in ECRHS I was significantly higher in group +/+ (2.1 kU/l) than in group +/– (0.78 kU/l) ($p < 0.01$).

Eighteen subjects (75%) in group +/+ and 4 subjects (20%) in group +/– displayed an IgE antibody level of ≥0.35 kU/l to one or more of the six allergens measured, but none in the control group ($p < 0.0001$, $p < 0.05$, respectively) (Table 4). Among group +/+, *L. destructor* was the most common allergen, with 16 (67%) positive subjects. Many of these were positive to more than one allergen; 13 were also positive to shrimp, 8 to cockroach, 4 to mosquito, 3 to tropomyosin 1 and 1 to blood worm. No correlation was found between the IgE value to *D. pteronyssinus* and the number of positive measurements to the other allergens.

DISCUSSION

In this study we examined what characterized the group of individuals in the ECRHS I, positive to specific IgE to *D. pteronyssinus* in an area with practically no HDM, and compared them with a group positive to specific IgE to timothy grass. Among the 89 selected for this follow-up study 28 had allowed home visits to search for HDMs without a single mite being found. Seasonal variation is unlikely to explain these results as dust samples were collected over a ten-month period and mite allergens found were negligible. In the study men comprised 75% of group +/+ but only 31% of the control group. In contrast similar prevalence of positive SPT to all allergens has been reported previously for both genders.[3]

Many cross-sectional studies in adult populations have reported decreasing prevalence of allergic sensitization with increasing age,[10] which may reflect the natural course of allergic sensitization or a cohort effect, *i. e.* increase in prevalence of allergic sensitization among younger birth cohorts. In our study 24 out of 49 that were positive to HDM in ECRHS I had become negative to HDM 8.4 years later while 4 individuals had become positive. Those who became negative had lower IgE values at ECRHS I (mean IgE 0.78 kU/l) compared with those who did not (mean IgE 2.1 kU/l). When all centres in ECRHS II are taken together no significant overall changes were found in the prevalence of IgE sensitization to HDM between ECRHS I and II.[6] In that sense Reykjavik differs from the average centre in the ECRHS II.

Specific IgE to *D. pteronyssinus* does not seem to reflect clinical symptoms in a dusty environment in contradiction to grass sensitisation in pollen-loaded areas. This lack of a clinically relevant association underlines the importance of caution when interpreting positive HDM results, at least in Iceland.

When seeking explanation for why so many are sensitive to HDM in HDM free environments we have three possibilities in mind: sensitisation may

Table 2 Positive answers to ECRHS II questionnaire (%)

	HDM sensitive		Grass sensitive
	Group +/+ N: 24	Group +/− N: 20	Group −/− N: 35
Have you had wheezing or whistling in your chest at any time in the last 12 months?	25	30	31
Have you ever had asthma?	29	40	37
Do you have any nasal allergies, including hay fever?	63	50*	83
Have you ever had eczema or any kind of skin allergy?	63	70	60
When you are in a dusty part of the house, or near pillows or duvets do you ever			
start to cough?	25	30	14
start to wheeze?	8	10	0
get a feeling of tightness in your chest?	17	15	9
start to feel short of breath?	13	10	9
get a runny or stuffy nose or start to sneeze?	50	25**	57
get itchy or watering eyes?	38	30	31
When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever			
start to cough?	13	30	37
start to wheeze?	13	10	17
get a feeling of tightness in your chest?	13	10	23
start to feel short of breath?	13	25	23
get a runny or stuffy nose or start to sneeze?	25***	30**	80
get itchy or watering eyes?	25**	35**	74

* $p < 0.05$, compared with the −/− group (Fisher's Exact Test)
** $p < 0.01$, compared with the −/− group (Fisher's Exact Test)
*** $p < 0.0001$, compared with the −/− group (Fisher's Exact Test)

Table 3 Positive answers to additional questions 2004 (%)

	HDM sensitive		Grass sensitive
	Group +/+ N: 24	Group +/− N: 20	Group −/− N: 35
Have you ever lived abroad?	29	35	43
Have you ever travelled abroad?	100	100	100
-mean number of travelling	25 (14−35)	23 (18−29)	26 (19−33)
Have you ever lived on a farm?	13	10	11
Have you ever dwelled on a farm during the summer vacation as a child/adolescent?	71*	40	40
Have you ever endeavoured horse riding?	21	20	6
Have you had clinical reactions when eating shellfish?	13	5	9
Have you had reactions to mosquito bites?	58	60	37
Have you owned or kept aquarium fishes?	75	50	63
-before 12 years of age	50 *	20	23
-after 12 years of age	46	45	54

* $p < 0.05$, compared with the −/− group (Fisher's Exact Test)

have occurred when travelling or living abroad, sensitisation may have occurred when travelling or living in other parts of the country, and the third possibility is that specific IgE to *D. pteronyssinus* may express cross-sensitisation to other allergens.

No relationship was found between sensitisation to HDM and staying outside Iceland. Group +/+ had dwelled significantly more often on farms during the summer vacation. It is a possibility that exposure to HDM on farms has led to sensitisation, as informa-

Table 4 Percent positive to specific IgE (≥0.35 kU/l)

	HDM sensitive		Grass sensitive
	Group +/+ N: 24	Group +/− N: 20	Group −/− N: 35
Allergen:			
L. destructor	67***	15*	0
Shrimp	58***	0	0
Cockroach	33**	0	0
Mosquito	17*	0	0
Tropomyosin	17*	5	0
Blood worm	4	0	0
One or more positive	75***	20*	0

* $p < 0.05$, compared with the −/− group (Fisher's Exact Test)
** $p < 0.01$, compared with the −/− group (Fisher's Exact Test)
*** $p < 0.0001$, compared with the −/− group (Fisher's Exact Test)

tion about HDM in farmhouses is still not available.

In the middle of the last century, when the majority of the participants in the study were growing up, exposure to hay dust was very common among the urban population because of summer vacations on farms among youngsters, in particular boys. Exposure to hay can also be related to horse riding and horse feeding, which is a very popular hobby in Iceland. In ECRHS I, were participants came from Reykjavik and suburbs, 69% of all men and 31% of all women had been on farms during their summer holidays and 69% of participating men and 41% of participating women had handled hay at some time or been exposed to hay dust.[11] Of those who had been exposed to hay dust 21.5% reported some symptoms when exposed and 16.7% were positive to *L. destructor* (SPT ≥1 mm) compared with 7.8% among those not exposed to hay dust.[11] Among farmers in Iceland and their families storages mites, in particular *L. destructor*, are the main cause of atopy and atopic diseases.[12]

Previous studies have reported allergic cross-sensitivity between HDM and other arthropods, among them *L. destructor*.[13] *L. destructor* accounted for 25% of all storage mites found in Icelandic hay 1981.[14] Cross-sensitisation may also exist between HDM (Der p 10, Der f 10) and muscle protein, tropomyosin.[15] Similar proteins occur in a wide range of arthropods, including shrimps and lobsters.[15] Tropomyosins are also found in other invertebrates such as cockroaches, chironomids and mosquitoes.[15,16] RAST inhibition studies have shown that cross-sensitivity exists between *D. pteronyssinus* and both cockroaches and chironomids.[17,18] Bloodworms are chironomid larvae that are used as aquarium fish food, and allergy against them has been reported in persons handling them as fish food.[18] Cross-sensitisation has also been found between HDM, crustaceans and mosquitoes.[16,19] In our study, group +/+ was more exposed to hay dust environments than the control group, and kept aquarium fishes more often than the control group. Group +/+ had also more often symptoms after eating shellfish or after mosquito bites, although these differences were not significant. Our results, as demonstrated in Table 4, indicate that serum-specific IgE to HDM may be an expression of sensitisation to other allergens, cross-reacting to HDM. This is supported by negative findings for the same cross-reactive allergens in the control group of grass-sensitised individuals. The storage mite *L. destructor* is responsible for two thirds of these responses and there seems to have been some cross-sensitisation between all the allergens measured. The clinical relevance of these positive measurements is however questionable. In group +/+, 58% were shrimp positive; only 13% of them reported clinical reactions when eating shellfish compared with 9% in the control group. As shellfish is a common ingredient in the Icelandic diet, these results do not appear to express clinical allergy to shrimps. All but one of the 14 shrimp positive individuals were also positive to *L. destructor*.

Altogether, 17% in group +/+ had a specific IgE to the shrimp allergen tropomyocin, thus indicating that tropomyosin can only be responsible for a small part of the cross-sensitisation between *D. pteronyssinus* and shrimp. This is in contrast to previously reported cross-reactivity between HDM and crustaceans where tropomyosin has been reported to be the major cross-reactive allergen.[15,20]

Compared with none in the control group, 33% in group +/+ had specific IgE to cockroach and 17% to mosquito, even though there are neither mosquitoes nor cockroaches found in Iceland. These people might have been sensitised when living or travelling abroad, but this may as well be explained by cross-sensitisation. The fact that none in the control group

were positive to these allergens makes the latter alternative likely.

There is good evidence for a dose-response association between HDM exposure, HDM sensitisation and asthma.[21,22] Sensitisation to HDM has been considered to be a major independent risk factor for asthma in all areas where the climate supports mite growth.[23,24] In our study there was no tendency to bronchial hyperresponsiveness or asthma in group +/+ compared with the control group. This shows that allergy to HDM has little clinical relevance as such in Reykjavik. HDM sensitisation might, however, be a surrogate marker of a sensitisation to other allergens cross-reacting to HDM where the clinical relevance is not fully revealed.

In summary people in Reykjavik with specific IgE to *D. pteronyssinus* are more often men who spent time on farms in childhood and to day have a high prevalence of IgE antibodies cross-reactive to *D. pteronyssinus*, which indicates that IgE antibodies to HDM may be an expression of sensitisation to other allergens cross-reacting to HDM, supported by negative findings for cross-reacting allergens in the control group. It is also possible that exposure to HDM on farms has led to sensitisation, as information about HDM in farmhouses is still not available. Specific IgE to *D. pteronyssinus* does not seem to reflect clinical symptoms in dusty environments and we believe that a positive HDM test should be interpreted with precaution. Therefore, traditional recommendation to those with a positive specific IgE to HDM should only be put forward when based on the presence of clinical symptoms as well.

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